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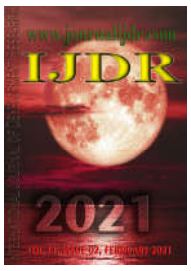

RESEARCH ARTICLE OPEN ACCESS

COVID-19 - RISKS TO THE CENTRAL NERVOUS SYSTEM AND CARDIOVASCULAR DAMAGE

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ABSTRACT

Coronavirus disease 2019 (SARS - COVID 2) still is a new virus for the scientific community however, it is crucial to try to understand at an early stage how covid-19 affects both the cardiovascular system and the possible of injuries that it can cause to the central nervous system. The aim of this article is to describe the degree of myocardial injury associated with covid-19-positive patients with more severe symptoms of the disease, as well as to understand whether the virus can penetrate the neurons, never neglecting the premise that neurological symptoms can have various causes. Also detail the relationship of the cardiovascular system with the central nervous system in cases such as anxiety that is common at the time of a pandemic.

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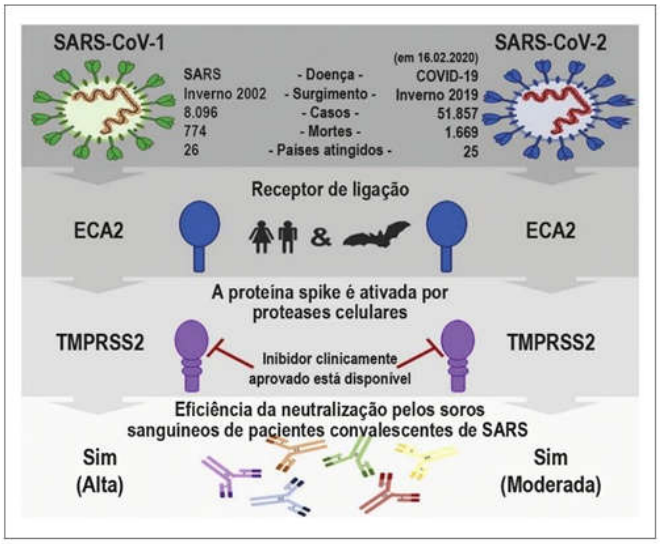
INTRODUCTION

Coronavirus disease_2019 (COVID-19) has rapidly become one of the most proliferating and deadly pandemics we have seen in modern history. The COVID-19 is caused by severe acute respiratory syndrome - Coronavirus-2 (SARS-CoV-2) and the mode of infection associated with it is directly related to the direct entry of the SARS-CoV-2 virus into cells through the receptor of the human angiotensin converting enzyme 2 (ACE2). This type of acute infection has its effects predominantly localized in the lungs, but also in the entire cardiovascular system. In addition to the effects mentioned above, many of the symptoms reported by people infected with SARS-CoV-2 involve the nervous system. Patients often describe headaches, muscle and joint pain, fatigue and "brain fog". There are also fairly continuous reports of loss of taste and smell, and these symptoms can last for weeks or even months after infection. In more severe cases, COVID-19 can also lead to encephalitis or stroke. It is therefore irrefutable

that COVID-19 affects the central nervous system and has undeniable neurological effects.



STUDY

Although pulmonary manifestations are its most common consequence, COVID-19 causes systemic inflammation with varying presentations of cardiac involvement as well. Very recently, the Journal of the American College of Cardiology conducted a multi-hospital retrospective study involving a sample of 3000 patients, of both sexes and different age groups, who were hospitalized with COVID-19 infection. In that same study it was concluded that:

- Myocardial injury is common among patients hospitalized with COVID-19, but is more often mild, associated with a low elevation of troponin concentration level;
- A more significant myocardial injury may be associated with more than a triplication of the mortality risk;
- COVID-19 patients with a history of CVD are more susceptible to myocardial injury than patients without CVD, but without obvious corroborating evidence of primary acute myocardial infarction;

The first country to detect the SARS- CoV2 virus was China, where it is thought to have been the initial focus of the pandemic. Myocardial damage was detected in patients in this country from which a sample (138) was selected, with enlarged cardiac biomarkers.

> *In a study involving 138 patients with COCID-19 in Wuhan, cardiac damage with highly sensitive troponin I (hs-cTnI) and ECG or echocardiographic abnormalities were generally present in 7.2% of patients and in 22% of patients requiring intensive care. The Chinese national health report showed that approximately 12% of patients without CVD saw their troponin levels increased or an increase in cardiac arrest rates during hospitalization. In particular, hs-cTnI was above the 99th percentile reference limit in 46% of survivors. (TANRIVERDI and ASKIN 2020)*

It is therefore pertinent and necessary to recognize acute myocarditis as a complication associated with COVID-19. This data allows for a more targeted follow-up of the patient with the awareness of the existence of these complications.

> *Myocardial injury has fatal consequences for COVID-19. Patients with a history of coronary artery disease without myocardial injury have a relatively better prognosis. Myocardial damage triggers cardiac dysfunction and arrhythmias. Inflammation is one of the possible causes of myocardial injury. Closer follow-up and multiple treatment regimens should be considered for patients at high risk of myocardial injury. Cardiac damage has been common among hospitalized patients with COVID-19 and is closely related to the risk of hospital mortality. Further research will be needed to clarify the mechanism of cardiac injury, and complications should be carefully monitored in treatment with COVID-19. (TANRIVERDI and ASKIN 2020)*

In the article Analysis of myocardial injury in patients with COVID-19 and association between concomitant cardiovascular diseases and severity of COVID-1, the authors observed that in addition to the previously reported, male patients, with advanced age and/or patients with diseases related to high ECA2 expression (e.g., hypertension, diabetes, chronic obstructive pulmonary disease (COPD)) presented worse prognosis when exposed to COVID-19. At the neurological level, laboratory studies using rats and also human brain tissue samples have recently been carried out where it has been observed that SARS-CoV-2 has the ability to penetrate nerve cells and the brain, although it is not yet fully understood which conditions are essential for this to happen. In other words, it is not known whether it happens routinely or only in the most severe cases as the immune system goes into over-exploitation. That said, the effects can be broad-spectrum, causing even the immune cells to invade the brain and causing significant damage.

In particular, the most persistent neurological symptoms in positive SARS-CoV2 patients tend to be less severe, but not so easy to uncover and complete a unique clinical picture. Many patients, even after discharge and the main (more physical) symptoms have dissipated, experience a number of relevant indicators. Many of them experience memory loss (of varying lengths), disorientation and other mental confusion. What underlies these experiences is not yet clear, although they may also derive from the widespread inflammation that can accompany COVID-19. Many people, however, develop mental fatigue and confusion that lasts for months, even after a mild case that does not necessarily stimulate the immune system to get out of control.

• The clinical syndromes reported were classified as vascular brain event, mental state alteration, peripheral neurology and others. For each of these classes pre-defined criteria were established, as well as the possibility of assigning more than one class to the same patient:
• vascular brain event: ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage, venous sinus thrombosis, cerebral vasculitis.
• Alteration of mental state: encephalopathy, encephalitis, convulsions, neuropsychiatric syndromes (psychosis, neurocognitive syndrome similar to dementia, personality changes, catatonia, anxiety, depression, chronic fatigue syndrome and post-traumatic stress);
• Peripheral neurology: Guillain Barré syndrome, Miller Fisher syndrome, neuritebrachial, myasthenia gravis, peripheral neuropathy, myopathy, myositis, neuromiopathy of the critically ill;
• Others: for those not corresponding to the previous classes.
(PATROCLO 2020)

Another symptom that occurs frequently is anosmia, or loss of smell. The loss of the ability to feel and distinguish smells can originate in changes that happen without the nerves themselves becoming infected. As is well known, olfactory neurons, the cells that transmit odors to the brain, lack the primary coupling site, or receptor, for SARS-CoV-2, and so far there has been no scientific evidence to prove their ability to suffer infection. The scientific community is still investigating how the loss of smell may result from an interaction between the virus and another receptor in the olfactory neurons or from its contact with non-neural cells that line the nose. In this way, we can conclude that the virus does not need to spread within the neurons to cause some of the mysterious neurological symptoms that now emerge from the disease.

Many pain-related effects, for example, can arise from an attack on sensory neurons, the nerves that extend from the spinal cord throughout the body to collect information from the external environment or from internal body processes. Researchers are now making progress in understanding how SARS-CoV-2 could divert pain-sensitive neurons, called nociceptors, to produce some of the characteristic symptoms of COVID-19. Theodore Price, a scientist at the University of Dallas (Texas), have pain like is main target of study and decided to carry out a study in this field in patients affected with COVID-19. Pointing out that although initial common symptoms such as sore throat, headaches, muscle pain throughout the body and severe cough are more prevalent, there are other curious symptoms that allow some considerations. Some patients hospitalized with COVID-19 report a loss of a particular sensation, in this case in particular they say they are unable to detect spicy peppers or fresh pepper - perceptions transmitted by nociceptors, not taste cells. Although many of these effects are typical of viral infections, the prevalence and persistence of these pain-related symptoms - and their presence even in mild cases of COVID-19 - suggests that sensory neurons may be affected beyond the normal inflammatory responses to the infection. This means that the effects may be directly linked to the virus itself, and this observation led him to investigate whether the new coronavirus could infect the nociceptors. To determine whether SARS-CoV-2 can infect cells throughout the body, the scientific community has determined that the main criterion is the presence of the converting enzyme angiotensin 2 (ACE2), a protein incorporated in the surface of cells. ACE2 acts as a receptor that sends signals to the cell to regulate blood pressure and is also an entry point for SARS-CoV-2. Now the goal was to look for evidence that it could be present in human neurons. Nociceptors, as well as other sensory neurons are grouped in discrete groups, found even outside the spinal cord, called dorsal root ganglia (DDRG). Price and his team obtained donated nerve cells after death or cancer surgeries, and later the researchers performed sequencing of the RN. This is a technique to determine what proteins a cell is about to produce by using antibodies to target the ACE2 itself. They discovered that a subset of DRG neurons contained ACE2, providing the virus with a portal for the cells.

Sensory neurons have long links called axons, whose endings feel specific stimuli in the body and then transmit them to the brain in the form of electrochemical signals. The specific DRG neurons that contained ACE2 also had the genetic instructions, mRNA, for a sensory protein called MRGPRD. This protein marks cells as a subset of neurons whose endings are concentrated on the surfaces of the body - the skin and internal organs, including the lungs - where they would be positioned to capture the virus.

In this way the nerve infection can contribute to acute as well as lasting symptoms.

> *"The most likely scenario would be that the autonomic and sensory nerves would be affected by the virus. We know that if the sensory neurons are infected by a virus, it can have long-term consequences even if the virus does not remain in the cells, it does not need the neurons to be infected. In another recent study, I compared genetic sequencing data of lung cells from patients with COVID and healthy controls and looked for interactions with healthy human DRG neurons. We found many immune system signaling molecules called cytokines from infected patients that could interact with receptors in neurons. It's basically a lot of things that we know are involved in neuropathic pain, suggesting that nerves may be suffering lasting damage from immune molecules without being directly infected by the virus".* (PRICE 2020)

More recently, studies are being developed that intend to relate the nervous system with the cardiovascular system. It is the broadening of an integrated view of neuroscience with the cardiovascular system and how mental pathologies can affect other vital systems, such as the cardiovascular system in situations like the current pandemic.

> *"Life consists of a dynamic balance, constantly alternating states of stress and homeostasis. In this way, the forces that alter homeostasis are balanced by adaptive responses generated by the organism. Multicellular organisms adapt to these situations through complex neural, humoral and cellular alterations, involving multiple organs and tissues. The human organism has developed a complex system, consisting of components of the central nervous system, including the neurons of the hypothalamic paraventricular nucleus, which produce the release hormone of corticotrophin, noradrenergic nuclei of the brain stem with its peripheral components, the hypothalamo-hypophysis-adrenal axis and the autonomous nervous system, whose main function is to maintain homeostasis at rest and in stress situations. This system exerts an important influence on many vital functions, such as breathing, cardiovascular tone and intermediate metabolism, which are also altered by stress states".* (LOURES et all)

Loures et all, in the article mental stress and cardiovascular system describe some essential points that are worth mentioning.

> *"Mental stress and myocardial ischemia - Epidemiological studies relate emotional stress to morbidity and mortality in coronary atherosclerotic disease. The extensive literature on the subject includes the chronic and acute effects of stress, such as social isolation, occupational stress, prognosis after acute myocardial infarction in patients with depression and precipitation of acute cardiac events. The presence of mental stress induced ischemia is associated with a significant increase in the frequency of fatal or non-fatal cardiac events, regardless of age, ejection fraction, previous acute myocardial infarction and events caused by stress induced ischemia. Mental activity seems to be as potent as physical activity in determining transient myocardial ischemia, having a wide correlation with circadian rhythm.*
>
> *Coronary flow, myocardial perfusion and cardiac arrhythmias - The participation of mental stress in ischemic myocardial disease is done in two ways: as a risk factor for coronary artery disease and as a trigger for acute ischemic events in patients with established coronary atherosclerosis. Chronic exposure to stress would lead to an exacerbation of all the vascular changes and intermediate metabolism induced by it. Such alterations, especially platelet and lipid alterations, have a strong atherogenic character. The pathogenesis of changes induced by acute exposure to mental stress refers mainly to myocardial ischemia and the presence of arrhythmias. There are two possible mechanisms responsible for the development of myocardial ischemia, in the presence of coronary atherosclerotic disease, during mental stress: the increase in coronary vasomotor tonus with decrease in coronary flow and the sympathetic hyperactivity that determines an increase in heart rate, blood pressure and myocardial contractility leading to an increase in myocardial oxygen consumption. Vagal hypoactivity, independently, also correlates with higher cardiovascular morbidity and mortality, through a decrease in ventricular fibrillation threshold, an increase in heart rate and a decrease in pre-synaptic adrenergic modulation. The specific performance in parasympathetic dysfunction, for example, through the use of the anticholinesterasic drug pyridostigmine, has changed favorably important prognostic markers for cardiovascular disease in normal individuals. Specifically in relation to mental stress, cholinergic stimulation with pyridostigmine was able to inhibit the increase of the double-product. Mental stress induced ischemia is more often silent, occurring with a minor double-product when compared to physical stress induced ischemia. Ischemic events occur with a lower heart rate and the increase in diastolic pressure during mental stress is greater than that obtained during stress testing, with no significant difference in relation to systolic pressure. These facts show the probable participation of the primary reduction in coronary flow, associated with an increase in metabolic demand, induction of ischemia by mental stress. There is angiographic evidence of coronary vasoconstriction at the site of atherosclerosis during*

arithmetic test performance. More recently, endothelial dysfunction has been described as a potential contributor to the development of coronary spasm by reducing the secretion of the endothelial relaxation factor. Catecholamines are potent vasoconstrictors due to their direct effect on the smooth musculature of the vessels. However, in vitro studies have shown that catecholamines, especially norepinephrine, also cause coronary artery vasodilation. This paradoxical vasodilatation in normal arteries seems to be mediated by the endothelium, through the stimulation of a2 adrenergic receptors, which promote the release of nitric oxide. This effect opposes the direct vasoconstrictor effect. In individuals with coronary artery disease, endothelial injury prevents these events. The association of mental stress with arrhythmic events is related to sympathetic hyperactivity and a reduction in parasympathetic activity, besides the presence of ischemia. These alterations would favor myocardial electrical instability, leading to the development of lethal ventricular arrhythmias.

Mental stress and ventricular function - Mental stress also significantly affects myocardial function. In patients with left ventricular dysfunction (decrease in the ejection fraction greater than or equal to 5%), during the mental stress test, there is a greater increase in heart rate, cardiac output, blood pressure and peripheral vascular resistance, when compared to those who did not develop left ventricular dysfunction during stress. There is, therefore, a correlation with increased epinephrine 31 secretion. Ischemia developed during mental stress correlates with a higher reactive increase in peripheral vascular resistance than with increased heart rate and cardiac output, when compared to effort-induced ischemia. Mental stress induced ischemia is accompanied by diastolic dysfunction, increased left ventricular volume and a reduction in the left ventricular ejection fraction, which occurs with the onset of stress, with a rebound immediately after its end. The reduction of the ejection fraction can be attributed to the increase of the post-load imposed on the left ventricle, to the reduction of contractility or to both, not being related to heart rate, blood pressure, cardiac output, gender or age. It has been observed that the segmental alterations in echocardiography, alterations in myocardial scintigraphy and the decrease in the ejection fraction during mental stress in patients with coronary atherosclerotic disease, determine an increase in the risk of developing cardiac events in one year and a greater association with episodes of silent ischemia". (LOURES et all)

We may then conclude that mental stress and anxiety can serve as an ignition for cardiovascular disease, both in its chronic and acute form. The physiological changes they can cause, especially in hemostasis and intermediate metabolism reveal this characteristic to us. It is also pertinent to make a reference to sympathetic hyperactivity and the vagal inhibition that stress triggers. In this case and when observed, it causes an imbalance in the performance of the autonomous nervous system which may be responsible for causing ischemic and arrhythmic events, more important in the presence of endothelial dysfunction. At the level of mental health, the anxiety and fear that are inherent to the entire pandemic situation will trigger negative responses at the brain level and with orders of complexity that vary greatly in scale. In addition to the fear of contracting the disease, there is a constant feeling of insecurity allied obviously to the fear that the resources will not be sufficient to fight this pandemic effectively. In addition, the social distance imposed and the deprivation of contact with family members have a considerable impact on society and the way it is managed and built. Public health authorities should be alert so that the COVID-19 pandemic does not develop later into a mental health pandemic in disintegrated and destructured societies.

The management of this problem has to be built according to the moment and adapting strategies to each of the different phases: pre-crisis, intracris and post-crisis. Ten months after the beginning of this health crisis, the most reported effects of isolation and quarantine measures include symptoms of post-traumatic stress, confusion and anger, a feeling of loneliness and apathy towards reality that cause enormous losses in terms of psychological wellbeing, as well as the Burnout syndrome, (a condition of physical and mental exhaustion associated with professional life).

CONCLUSION

As can be observed throughout this article and taking into consideration the data presented, at the cardiovascular level, myocardial injury is prevalent, usually at low levels, among patients with COVID-19 with more acute crises and is associated with worse results. The history of CVD was associated with myocardial injury in the COVID-19 infection scenario. At the neurological level, although there is still no irrefutable scientific evidence that the direct entry of the virus into nerve cells is the main mechanism that causes damage at the cellular level, the scientific community should not disregard this possibility. On the other hand, there is a great possibility that inflammatory conditions external to nerve cells may alter their activity. In the worst case scenario they may even cause permanent damage.

In another perspective of approaching the issue is the possibility that the interaction between the viral particles and the neurons themselves can lead to an autoimmune attack on the nerves. Taking into consideration that any and all pathogens that interfere with the neurons cause irreversible damage even if the neurons are not so significant, we come to the conclusion that COVID-19 by affecting the independent neurons cause irreversible traumas that affect the cognition and may result in a disorder, syndrome or other future variables. In order to know the types of consequences, we will only be able to evaluate in the future people who have already suffered from the disease. The same happens with the lungs and cardiovascular system, which may increase the chances of diseases such as infarction, heart failure, stroke, among others. The final part of the article only intends to focus on a theme that is sometimes forgotten in this context of a pandemic and that many damages may be caused in the near future, both at the social level in a broader sense of the issue and, in a more restricted sense regarding specific groups such as health professionals.

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